

CLAIMS

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1. A method for controlling or up-regulating the availability or activity of a protein comprising regulating binding of the ubiquitin/proteasome system at a ubiquitin/proteasome system binding site of said protein.

5 2. A method according to claim 1 wherein said binding site comprises the amino acid sequence motif $\times\text{EFI}\text{xxDx}$ or a sequence essentially corresponding thereto, wherein D is the amino acid aspartic acid, E is the amino acid glutamic acid, F is the amino acid phenylalanine, I is the amino acid isoleucine and X is any other amino acid.

10 3. A method for controlling the availability and/or signal transduction capability of a cell surface receptor comprising providing an inhibitor capable of inhibiting proteolytic cleavage of said receptor.

15 4. A method according to claim 3 wherein said inhibitor is capable of inhibiting proteolytic cleavage of an intracellular part of said receptor.

5 20 5. A method according to claim 3 wherein said inhibitor is capable of inhibiting proteolytic cleavage of an extracellular part of said receptor.

6. A method according to anyone of claims 3 to 5 wherein said receptor is a hormone receptor, preferably selected from a group consisting of amino acid derivative, prostaglandine, peptide or protein hormone receptors.

25 7. A method according to claim 6 wherein said receptor is a growth hormone receptor.

8. A method according to any one of claims 1 or 2 wherein said protein is a transport protein.

9. A method according to claim 8 wherein said transport 30 protein is Glut4 insulin regulated glucose transporter.

10. A (poly)peptide or (poly)peptide analogue or mimeticum that is derived from, competes with or binds to an amino acid

sequence located at or around a ubiquitin/proteasome system binding site located in a protein.

11. A (poly)peptide or (poly)peptide analogue or mimeticum according to claim 10 wherein said binding site comprises the,

5 amino acid sequence motif xEFIxxDx or a sequence essentially corresponding thereto, wherein D is the amino acid aspartic acid, E is the amino acid glutamic acid, F is the amino acid phenylalanine, I is the amino acid isoleucine and X is any other amino acid.

10 12. An inhibitor capable of inhibiting proteolytic cleavage of a cell surface receptor for use in a method according to anyone of claims 1 to 7.

13. An inhibitor according to claim 12 which is capable of inhibiting proteolytic cleavage of the intra-cellular part of 15 said receptor.

14. An inhibitor according to claim 13 selected from the group of proteasome inhibitors, such as MG132, carboxybenzyl-leucyl-leucyl-leucinal, lactacystin, carboxybenzyl-leucyl-leucyl-leucyl vinylsulfone or the β -lacton form of lactacystin.

15. An inhibitor according to claim 13 comprising a (poly)peptide or (poly)peptide analogue or mimeticum that is derived from, competes with or binds to an amino acid sequence located at or around a ubiquitin and/or

20 ubiquitin/proteasome system binding site located in the intra-cellular part of a cell-surface receptor.

16. An inhibitor according to claim 15 wherein said binding site comprises the amino acid sequence motif xEFIxxDx or a sequence essentially corresponding thereto, wherein D is the 30 amino acid aspartic acid, E is the amino acid glutamic acid, F is the amino acid phenylalanine, I is the amino acid isoleucine and X is any other amino acid.

17. An inhibitor according to claim 16 wherein said binding site comprises the amino acid sequence DDSWVEFIELDI or

35 DSWVEFIELD.

18. An inhibitor according to claim 12 capable of inhibiting proteolytic cleavage of a extra-cellular part of said receptor.

19. An inhibitor according to claim 18 wherein said extra-cellular part comprises a approximately 60 kDa fragment of a extra-cellular domain of the growth hormone receptor.

20. An inhibitor according to claim 18 or 19 comprising a (poly)peptide or (poly)peptide analogue or mimeticum that is derived from, competes with or binds to an amino acid sequence located at or around a proteolytic cleavage signal site located in a extra-cellular part of said receptor.

21. An inhibitor according to claim 20 wherein said cleavage signal site comprises the amino acid sequence CEEDFYR or a sequence essentially corresponding thereto.

22. A (poly)peptide or (poly)peptide analogue or mimeticum that is derived from, competes with or binds to an amino acid sequence located at or around a ubiquitin and/or ubiquitin/proteasome system binding site located in the intra-cellular part of a cell-surface receptor.

23. A (poly)peptide or (poly)peptide analogue or mimeticum according to claim 22 wherein said binding site comprises the amino acid sequence motif $xEFIx_{xx}Dx$ or a sequence essentially corresponding thereto, wherein D is the amino acid aspartic acid, E is the amino acid glutamic acid, F is the amino acid phenylalanine, I is the amino acid isoleucine and X is any other amino acid.

24. A (poly)peptide or (poly)peptide analogue or mimeticum that is derived from, competes with or binds to an amino acid sequence located at or around a proteolytic cleavage signal site located in the extra-cellular part of a receptor.

25. A (poly)peptide or (poly)peptide analogue or mimeticum according to claim 24 wherein said cleavage signal site comprises the amino acid sequence CEEDFYR or a sequence essentially corresponding thereto.

26. A pharmaceutical composition comprising an inhibitor according to any of claims 12-21 or a (poly)peptide or

(poly)peptide analogue or mimeticum according to any of claims 10, 11 or 22-25.

27. A pharmaceutical composition according to claim 26 for regulating the activity of a hormone.

5 28. A pharmaceutical composition according to claim 27 for administering in conjunction with a hormone.

29. Use of an inhibitor according to any of claims 12 to 21 or a (poly)peptide or (poly)peptide analogue or mimeticum according to any of claims 10, 11 or 22-25 for the production 10 of a pharmaceutical composition for controlling the availability and/or signal transduction capability of a cell surface receptor.

15 30. Use according to claim 29 for the production of a pharmaceutical composition regulating the activity of a hormone.

31. Use according to claim 29 or 30 wherein said composition is administered in conjunction to the administration of said hormone.

20 32. Use according to any of claims 29 to 30 for the production of a pharmaceutical composition for the treatment of muscle wasting.

33. A method to control or up-regulate hormone activity by using an inhibitor according to any of claims 12 to 21 or a pharmaceutical composition according to any of claims 26 to 25 28.

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